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DISCUSSION

Dr Ronald Dalman (*Palo Alto, Calif*). If I understand your presentation correctly, it looks like STAT [signal transducer and activator of transcription] expression is protective against aneurysm progression; the double knockout seems to increase the rate of enlargement. This seems somewhat contradictory to the hypothesis that led you to explore this mechanism in the first place. Perhaps you can comment on this apparent discrepancy?

Dr Matthew J. Eagleton. Absolutely. When I started initially evaluating STAT1, my hypothesis was that loss of STAT1 would be associated with aneurysm inhibition. That hypothesis proved to be false and the opposite to be true. Some of our cellular work, not presented here, demonstrates that if we inhibit STAT1 in smooth muscle cells and macrophages, we see increased MMP [matrix metalloproteinase] expression and activity in those cells in response to stimulation, and so STAT1 may have a protective role in some way by inhibiting MMP expression.

I am not sure though in this model if it is just through regulation of MMP expression that STAT1 is working. I am concerned with the acuity with which the dissections occur, and we are considering that there may be some architectural alteration in the aortic wall associated with the loss of STAT1. We have not, however, been able to identify that alteration that would make the aorta in these double knockout mice more susceptible to an aortic dissection.

Dr Dalman. Do you use a normal chow diet or a high-fat chow diet?

Dr Eagleton. These mice are all on a normal chow diet.

Dr Dalman. And the cellularity; is there a difference at all in the inflammatory cell infiltrate (macrophages/neutrophils) that you see in the double knockouts vs the single knockouts?

Dr Eagleton. We have not yet done the morphometric analysis to look at cell numbers.

Dr Anton Sidawy (*Washington, DC*). The STATs are transcription activators that get phosphorylated in the cytoplasm but then move to the nucleus to exert their effect on the gene. Are there any published data that indicate that this process can get altered leading to formation of aneurysms in human?

Dr Eagleton. Not in humans. Most of the work done in humans to date, except for one article that begins to investigate its role in atherosclerosis, has been done in tumor biology.

Dr Sidawy. And why the female gender is protective?

Dr Eagleton. It's a great question and I don't know.

Dr B. Timothy Baxter (*Omaha, Neb*). One of the things about the animal models is that findings may be irrelevant to our patients. You started with the patient tissue, you found a protein of interest, and then looked at an animal model to see what this protein is doing. And you found out it was doing something quite different than what you thought. Beginning with human tissue is essential to assure relevance of work done in animal models. So I want to congratulate you on that. We now know that there are many gene knockout mice that don't get aneurysms. So my question is how are we going to find out which of these proteins are really critical?

Dr Eagleton. Great question. I think what we may ultimately have to do is look at a number of these knockout mice, perhaps do an array analysis on them, and see if there are any downstream effects that are similar between all of the mice that don't form aneurysms and is there a distal common pathway, or pathways, that are being affected and perhaps that is the area that needs to be focused on, or several pathways that need to be focused on.